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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/930,480	01/21/1998	LAURENT BRACCO	ST95021-US	3058

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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/930,480	BRACCO ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,61-63,65,72,74,76,77,79,80,92,93,95-97 and 105-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58,61-63,65,72,74,76,77,79,92,93,95-97 and 105-107* is/are rejected.

7)☒ Claim(s) *80* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

All objections and rejections not repeated in the instant Action have been withdrawn due to applicant's response to the previous Action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 58, 61-63, 65, 76-77, 92-93, 95-97, and 105-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al (U.S. Patent No. 5,650,298) in view of Whitlow et al (U.S. Patent No. 5,990,275). This rejection is maintained for reasons of record set forth in the paper mailed 5/7/03. Applicants' arguments filed 2/3/04 have been fully considered but they are not deemed to be persuasive.

Bujard et al teach a system for regulating expression of eukaryotic genes using components of the Tet repressor/operator/inducer system of prokaryotes. In the system of the invention, transcription of a nucleotide sequence operably linked to at least one tet operator sequence is stimulated by a tetracycline (Tc)-controllable transcriptional activator fusion protein (referred to herein as tTA). The tTA

is comprised of two polypeptides. The first polypeptide is a (full length) Tet repressor (TetR; e.g., a Tn10-derived tetR), which binds to tet operator sequences in the absence but not the presence of Tc. The second polypeptide directly or indirectly activates transcription in eukaryotic cells (columns 1-2). The second polypeptide can be a domain (e.g. dimerization domain) which recruits a transcriptional activator (e.g. an endogenous transcriptional activator) to interact with the tTA fusion protein by protein-protein interaction (e.g., a non-covalent interaction) (column 2). This reads on the claimed bispecific chimeric molecule because the fusion protein of TetR with a second polypeptide which indirectly activates transcription by recruiting an endogenous transcriptional activator is done through binding and the endogenous transcriptional activator is characteristic of at least a physiological state (the activation of the gene(s) regulated by that endogenous transcriptional activator) and the absence of that endogenous transcriptional activator means that the genes normally regulated by that activator are not and thus that lack of activation is a physiopathological situation.

Bujard et al also teach a system comprising the tTA and a Tet operator sequence (the regulatory sequence the tTA binds to, which comprises SEQ ID NO:1), a minimal promoter comprising at

least a portion of the CMV IE promoter or Tk promoter (both of which comprises a TATA box) and a gene, all operably linked reading on an expression cassette, wherein binding of the tTA activates transcription (columns 12-14 and columns 62-63). Bujard et al also teach that the linkage between the components of the fusion protein can be done using any means that preserves the function of each polypeptide (column 11).

Bujard et al do not specifically teach use of an arm consisting of from about 5 to 20 amino acids, such as SEQ ID NO:5 in linking the DNA binding domain and the second polypeptide.

Whitlow et al teach the use of peptide linkers (18-50 amino acids in length) for connecting polypeptide constituents together into a fusion polypeptide (abstract). The purpose of the linker is to provide greater stability and decreased susceptibility to aggregation (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the peptide linkers taught by Whitlow et al, or any other linkers known in the art, such as SEQ ID NO:5, in making the fusion tTA protein taught by Bujard et al because Bujard et al teach making fusion proteins between a DNA binding domain and a polypeptide that binds with a transactivator, linking them using any means taught

that preserves the function of each polypeptide, and Whitlow et al teach the use of peptide linkers of 18 to 50 amino acids for connecting polypeptide constituents together into a fusion polypeptide.

One would have been motivated to do so for the expected benefit of providing greater stability and decreasing susceptibility to aggregation as taught by Whitlow et al for the tTA taught by Bujard et al. Based upon the teachings of the cited the references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the peptide arm between the two domains that confer sufficient flexibility to the molecule in order to permit each of the domains to act autonomously) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26

USPQ2d 1057 (Fed. Cir. 1993). What is claimed is merely an arm consisting of from 5 to 30 amino acids that links the DNA binding domain with the regulatory domain. There is no specific limitation claimed concerning flexibility or function. Although Bujard et al do not specifically teach an arm (which is more commonly referred to as a linker or spacer), the reference **does** teach that the linkage between the components of the fusion protein can be done using any means that preserves the function of each polypeptide (column 11). This clearly shows that Bujard et al is teaching one of ordinary skill in the art to use any art-recognized linker between the two domains as long as the linker does not impair the function of either domain. The teachings of Whitlow et al are the teachings relied upon for the art-recognized linkers that are advantageously used in conjunction with the teaching of Bujard et al to use any linker that maintains the function of the domains. The instant rejection is based upon the obviousness of combining the teachings of the cited references to result in the claimed invention. The argument that Bujard et al teaches or suggests nothing with respect to the use of a hinge or arm in the claimed molecule is simply not persuasive because in the instant rejection, Bujard et al is not relied upon for the teachings of the specific type of linker, only that a linker can be used.

In response to applicant's argument that the arm is taught by the specification in order to confer sufficient flexibility for the two domains of the molecule so that the domains can function autonomously, which is different from the teachings of Whitlow that the linker provides greater stability and decreased susceptibility to aggregation, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Therefore, in light of all available evidence, including the rejection set forth above and in the previous Office Action, the applicant's arguments and the arguments set forth above, the claimed invention is still considered to be obvious over the teachings of the cited references and thus the instant rejection is properly maintained.

Claims 58, 61-63, 65, 72, 74, 76-77, 79, 92-93, 95-97, and 105-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al (U.S. Patent No. 5,650,298) and Whitlow et al (U.S. Patent No. 5,990,275) as applied to claims 58, 61-63, 65, 76-77, 92-93, 95-97, and 105-107 above, and

further in view of Hupp et al (Applicant reference PC), and Mezes et al (U.S. Patent No. 5,892,020). This is a new rejection necessitated by the applicant's amendment of the claims filed 2/3/04.

The teachings of Bujard et al and Whitlow et al are set forth above and applied as before.

Bujard et al do not specifically teach the domain in tTA which binds to a transactivator as being an antibody, specifically a single chain antibody, or the DNA-binding domain is at the C-terminus and the transactivator-binding domain is at the N-terminus.

Hupp et al teach monoclonal antibody pAb421, which binds p53 and activates p53 (abstract; Results section). p53 is taught as being a cellular protein that is involved in sequence-specific binding/transcriptional activation in cancer (page 875).

Mezes et al teach construction of single-chain antibodies from multi-chain antibodies, which allow for the construction of an antibody fragment which has the specificity and avidity of a whole antibody but are smaller in size, and can be easily expressed by expression vectors (columns 1-6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the tTA system

made obvious by the teachings of Bujard et al and Whitlow et al by using single chain monoclonal antibody as the domain that binds to the transactivator, as taught by Mezes et al, using as a basis for the antibody pAb421, which Hupp et al teaches binds to p53, a transactivator protein involved in cancer, because Bujard et al teaches that it is within the ordinary skill in the art to use any domain in tTA which indirectly interacts with a transcriptional activator by binding, Mezes et al teach that it is within the ordinary skill in the art to construct single-chain antibodies from multi-chain antibodies which has the specificity and avidity of a whole antibody and which can be expressed in expression vectors, and Hupp et al teaches a specific antibody that binds to p53 and endogenous transactivator involved in cancer, which binding activates p53.

One would have been motivated to do so for the expected benefit of making a tTA that activates the same genes as p53, which is involved in cancer, as taught by the combined teachings of the cited references. Based upon the teachings of the cited the references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

The applicant's arguments concerning Bujard et al and Whitlow et al were addressed above and equally apply to the instant rejection.

The applicant also argues that the teachings of Hupp et al are unrelated to the teachings of Bujard et al and Mezes et al because Bujard et al does not teach or suggest the use of an antibody in the transcriptional activator protein taught and Mezes et al is silent regarding the use of single-chain antibodies in a chimeric protein, and in fact teaches the antibodies for use in diagnostics and therapeutics, in the context of reaching their target tissue more rapidly, and are cleared more quickly from the body. It is argued by the applicant that in light of the great disparity among the teachings of the cited references, it is submitted that the Examiner has impermissibly utilized hindsight. The applicant's arguments are not persuasive for the following reasons.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Bujard et al was not relied upon for

the teachings of single-chain antibodies, the other two references were. Bujard et al **does** teach to use any domain in the fusion transactivator protein which indirectly interacts with a transcriptional activator by binding. Thus, this reference makes obvious the use of any art-recognized protein domain which binds to a transcriptional activator. The other two references were relied upon for the teachings of a specific protein domain which is encompassed by the teachings of Bujard et al: a single-chain antibody which binds to a transcription factor (and thus allows the selective recruitment of that factor) whose activation or inactivation leads to a physiopathological situation. The teachings of Hupp et al are not unrelated to the teachings of Bujard et al because Hupp et al teach the type of domain suggested by Bujard et al for use in the chimeric transactivator protein: a monoclonal antibody (which is a protein that constitutes a domain) which binds p53 (a transcriptional activator whose activation or inactivation leads to a physiopathological situation). Thus, the teachings of Hupp et al are very relevant to the teachings of Bujard et al. The teachings of Mezes et al are equally relevant because they teach that single-chain antibodies can have the specificity and avidity of a whole antibody but are smaller in size, and can be easily expressed by expression vectors, which is relevant to

the use of the monoclonal antibody of Hupp et al in the expression vectors taught by Bujard et al. Therefore, the instant rejection was not based upon impermissible hindsight reconstruction of the claimed invention, but instead the rejection was based upon the teachings of the cited references which in combination make obvious the claimed invention. The applicant did not address the precise basis of the rejection: the specific teachings in the art relied upon for selecting the components of the chimeric transactivator and thus the applicant's arguments are not persuasive.

Regarding the argument that Mezes et al is silent regarding the use of single-chain antibodies in a chimeric protein, and in fact teaches the antibodies for use in diagnostics and therapeutics, this argument is not persuasive because these teachings of Mezes were not relied upon for making obvious the claimed invention, the other teachings in the reference: construction of single-chain antibodies from multi-chain antibodies, which allow for the construction of an antibody fragment which has the specificity and avidity of a whole antibody but are smaller in size, and can be easily expressed by expression vectors, were the teachings relied upon. The fact that a reference has other teachings directed to things not directly relevant to the claimed invention is not a persuasive

argument to overcome a rejection based upon different teachings relied upon in the obviousness rejection because those teachings do not negate the teachings relied upon, unless those other teachings "teach away" from the invention, which is not the case here. It is clear that that the teachings of Mezes et al concerning single-chain antibodies are applicable to the monoclonal antibody of Hupp et al: the teachings of Mezes et al can be used to more easily express an antibody that binds p53 in an expression vector.

Therefore, in light of all available evidence, including the rejection set forth above and in the previous Office Action, the applicant's arguments and the arguments set forth above, the claimed invention is still considered to be obvious over the teachings of the cited references and thus the instant rejection is properly maintained.

Allowable Subject Matter

Claim 80 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone

numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Terry A. McKelvey

Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

May 3, 2004